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RESPONSE TO COMMENT ON SALOMON ET AL.

Gestational Diabetes Mellitus Is Associated With Changes in the Concentration and Bioactivity of Placenta-Derived Exosomes in Maternal Circulation Across Gestation. Diabetes 2016;65: 598–609

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We thank Patil et al. (1) for their interest in our article (2) in which we established the gestational profile of placental exosomes in the plasma of women with gestational diabetes mellitus (GDM). A prospective cohort of patients was recruited at three time points during pregnancy for this study; therefore, we analyzed plasma at early gestation (i.e., 11–14 weeks) before GDM was diagnosed. Currently, there is no reliable early detection biomarker to identify women who are at risk for developing GDM (3). We established that the total number of exosomes present in maternal plasma was ~twofold greater in women between 11 and 14 weeks who were subsequently identified as having GDM (diagnosed between 22 and 28 weeks) than women who experienced a normoglycemic pregnancy. We focused on a specific type of extracellular vesicles (EVs): the exosomes. We used the well-established and validated method of buoyant density centrifugation to obtain an enriched exosome fraction that minimized the contribution from other EVs. We agree that other types of EVs might be involved in the pathophysiology of GDM; however, protocols to specifically isolate different population of EVs are required.

The past decade has observed an extraordinary "explosion" of research in the field of EVs; however, advancement in the field is hindered by the lack of standardized isolation protocols. We agree that exosomes and microparticles (MPs) (also known as microvesicles) are different subpopulations of EVs. To our understanding, one of the biggest differences between exosomes and MPs is their biogenesis. MPs originate from the plasma membrane, and exosomes are a product of endosomal trafficking through multivesicular bodies and exocytotic release.

We agree that both placenta-derived exosomes and EVs may be of clinical utility as biomarkers and provide information about the cell/tissue of origin. The critical questions that need to be addressed to establish the value of these biomarkers are *1*) whether early pregnancy changes in the placental microenvironment affect the bioactivity of EVs in placental cells and *2*) whether these changes can be used as early biomarker for GDM. Previously published studies from our group have established that oxygen tension and high D-glucose concentrations increase the release of exosomes from first trimester trophoblast cells (i.e., at ~10 weeks of pregnancy) and modify their bioactivity on target cells (4,5). The effect of the microenvironment on the release and bioactivity of other EVs (e.g., MPs) from first trimester trophoblast cells remains to be established. Finally, we strongly believe that the field of vesicle-mediated cell-to-cell communication is a burgeoning field and may provide unique insights into

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the etiology of disease, early detection, and treatment monitoring.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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